Remarks

Claims 26, 28-31 and 33-35 are pending in the subject application.

Claims Rejected Under 35 U.S.C. §112, Written Description

The Examiner rejected claims 26, 28-31, and 33-35 as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." With respect to the four anti-PM1 monoclonal antibodies, PA-3, PA-5, PA-6, and PA-7 disclosed in the application, the Examiner stated that "All of these antibodies inhibited both JR-FL and LAI Env fusion-based events, albeit to different extents" and that "The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of anti-PM1 monoclonal antibodies that display preferential inhibitory activities towards NSI (JR-FL)-Env mediated events but not SI (Lai)-Env mediated events."

In response, applicants respectfully traverse the Examiner's rejection. Applicants initially note that the claimed method does not recite inhibiting JR-FL Env "fusion-based events", LAI Env "fusion-based events", or preferential inhibitory activities toward NSI (JR-FL)-Env mediated events but not SI (Lai)-Env mediated events. Therefore, the Examiner appears to be stating that an invention, other than the invention claimed by applicants, is not adequately described.

Applicants maintain that the invention actually claimed is adequately described. The method claimed in this application comprises "contacting the CD4+ cell with an anti-PM1 monoclonal antibody that (1) inhibits HIV-1 envelope glycoprotein mediated membrane fusion of HeLa-env_{JR-FL} to a PM1 cell, but (2) does not

inhibit HIV-1 envelope glycoprotein mediated membrane fusion of HeLa-env_{LAI} to a HeLa-$CD4^+$ cell." The data on page 61, Table 3, shows four exemplified monoclonal antibodies having the characteristics recited in the claims. (See Table 3, row 1, where PA-3, PA-5, PA-6 and PA-7 show, respectively, 85.3%, 96.3%, 92%, and 67% inhibition of HIV-1 envelope glycoprotein mediated membrane fusion of HeLa-env_{JR-FL} with a PM1 cell and row 5, where PA-3, PA-5, PA-6 and PA-7 show, respectively, 0%, 0%, 7.7%, and 0% inhibition of HIV-1 envelope glycoprotein mediated membrane fusion of HeLa-env_{LAI} to a HeLa-$CD4^+$ cell).

In addition, applicants also note that M.P.E.P §2163 states, with regard to written description of antibodies, that "For example, disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. Noelle v. Lederman, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004)". Applicants note that in the present case the antibodies recited in the method claimed are described as anti-PM1 antibodies. As described in the instant application on page 60, lines 9-15, "[h]ybridomas against PMI cells were generated and the supernatants from these hybridomas were screened in the RET assay to identify hybridomas which secrete antibodies capable of inhibiting fusion between HeLa-env_{JR-FL} to PM1 cells." This clear recitation of art-recognized PM1 cells as antigen/immunogen used to generate hybridomas secreting anti-PM1 monoclonal antibodies having the claimed function further supports the applicants' position that the written description requirement has been fulfilled.

Moreover, the antibodies recited in the claimed method are also characterized functionally, thus further describing them. Specifically, the claimed method recites using an antibody which "(1) inhibits HIV-1 envelope glycoprotein mediated membrane fusion of HeLa-Env_{JR-FL} to a PM1 cell, but (2) does not inhibit HIV-1

envelope glycoprotein mediated membrane fusion of HeLa-Env_{LAI} to a HeLa-CD4+ cell". The recited description is supported by the disclosure in the specification at, for example, the Third Series of Experiments on page 60, and in Table 3, page 61.

In summary, the antibodies recited in the claimed methods are (1) described by antigen binding (2) functionally described, and (3) are supported by working examples in the specification. Applicants maintain, therefore, that one skilled in the art would recognize that applicants had possession of the invention as claimed. Accordingly, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Claims Rejected Under 35 U.S.C. §112, Enablement

The Examiner rejected claims 26, 28-31, and 33-35 as allegedly not enabled by the specification.

The Examiner asserted that the disclosed PA-3, PA-5, PA-6 and PA-7 antibodies inhibited "both JR-FL and Lai Env-based fusion events", but that the claims "clearly require a Mab that is capable of inhibiting JR-FL Env fusion-based events, but not Lai Env fusion-mediated events."

In response, applicants respectfully traverse the Examiner's rejection. Applicants note that the claimed method does not recite inhibiting "JR-FL Env-based fusion events" and does not recite "Lai Env fusion-mediated events" (emphasis added in both quotes). Therefore, the Examiner appears to be stating that an invention, other than the invention claimed by applicants, is not enabled.

The method claimed in this application comprises "contacting the CD4+ cell with an anti-PM1 monoclonal antibody that (1) inhibits HIV-1 envelope glycoprotein mediated membrane fusion of HeLa-env_{JR-FL} to a PM1 cell, but (2) does not inhibit HIV-1 envelope glycoprotein

mediated membrane fusion of HeLa-env_{LAI} to a HeLa-$CD4^+$ cell." Applicants maintain that the invention actually claimed is enabled. In support of this, applicants address the Examiner's assertions individually as follows.

The Examiner stated that "the disclosure fails to provide adequate guidance pertaining to the structural/functional characteristics of the claimed genus of antibodies". The Examiner asserted that "the disclosure fails to identify the antigen(s) or epitope(s) of interest." The Examiner further asserted that the disclosure fails to provide any working embodiments, and also asserted that the "disclosure fails to provide a reproducible method for preparing antibodies with the recited characteristics."

Applicants note that the assertion regarding failing to identify an antigen is incorrect. The claims recite an "anti-PM1 antibody", i.e., an antibody which binds PMI cells, as clearly described in the instant specification (e.g., at page 60). Thus, the antigen to which the claimed antibody binds is clearly recited. The Examiner's assertion regarding the specification failing to provide any working embodiments is also incorrect. Indeed, the specification provides four examples of antibodies having the characteristics recited in the claim (See Table 3, row 1, where PA-3, PA-5, PA-6 and PA-7, respectively, show 85.3%, 96.3%, 92%, and 67% inhibition of HIV-1 envelope glycoprotein mediated membrane fusion of HeLa-env_{JR-FL} with a PM1 cell and row 5, where PA-3, PA-5, PA-6 and PA-7 show, respectively, 0%, 0%, 7.7%, and 0% inhibition of HIV-1 envelope glycoprotein mediated membrane fusion of HeLa-env_{LAI} to a HeLa-$CD4^+$ cell).

With regard to the Examiner's statements as to a reproducible method for preparing the antibodies with the recited characteristics, applicants submit that the method stated in the disclosure is effective to produce antibodies as described and claimed. The four working examples of monoclonal antibodies recited in the

specification are representative examples of a larger number of monoclonal antibodies which were produced by hybridomas isolated from the same fusion and screened using the RET assay. Applicants have detailed the larger number of monoclonal antibodies, which were produced by hybridomas isolated from the same fusion and screened using the RET assay, in arguments presented hereinbelow in relation to the Examiner's citing of *In re Wands*.

In Re Wands

Applicants maintain that, based on the decision in *In re Wands*, which is cited by the Examiner in the enablement rejection and which decision *specifically discusses hybridomas and monoclonal antibodies*, the claims are enabled.

Applicants agree with the Examiner's reliance on *In re Wands*, 8 USPQ2d 1400 (CAFC 1988), a copy of which is attached hereto as **Exhibit A**. In Wands, the CAFC discusses enablement in the context of hybridomas and monoclonal antibodies and the specific fact pattern in which 4 of 9 hybridomas tested produced antibodies falling within the claimed range (see page 1406, *In re Wands*). In *In re Wands*, the CAFC found the claims enabled. In fact, as recited in M.P.E.P. §2164.01(a) quoting *In re Wands*, "[t]he Court held that the specification was enabling with respect to the claims at issue" and found, *inter alia*, that there was "a high level of skill in the art at the time the application was filed;' and 'all of the methods needed to practice the invention were well known.' 858 F.2d at 740, 8 USPQ2d at 1406. After considering all of the factors related to the enablement issue, the court concluded that 'it would not require undue experimentation to obtain antibodies needed to practice the claimed invention.' Id., 8 USPQ2d at 1407."

Applicants note that the facts of the present case are analogous to those of *In re Wands*. Applicants note that 8 of 19 monoclonal antibodies produced by hybridomas and tested by applicants (i) inhibited fusion of HeLa-env_{JR-FL} and PM1 CD4+ cells, but (ii) did not

inhibit fusion of HeLa-env_{LAI} and HeLa-CD4+ cells. Four (4) of these 8 monoclonal antibodies are produced by the hybridomas designated PA-3, PA-5, PA-6 and PA-7 as recited in the specification. In this regard, applicants attach hereto as **Exhibit B** a copy of Declaration Under 37 C.F.R. §1.132 of Ms. Kirsten Nagashima, who tested these exemplified antibodies and other monoclonal antibodies, which Declaration was recently filed in co-pending application, U.S. Serial No. 11/258,963.

Specifically, in her Declaration, Ms. Nagashima describes that monoclonal antibodies produced by 8 of 19 hybridomas tested exhibited the required characteristics. More specifically, Ms. Nagashima declares that she prepared and isolated 2100 hybridomas from mice that had been immunized with PM1 cells and performed resonance energy transfer (RET) assays, as described in the above-identified application at page 61, line 20 to page 62, line 3, on supernatants from the hybridomas to select those hybridomas that produced and secreted monoclonal antibodies that inhibited fusion of HeLa-env_{JR-FL} with PM1 cells. After three screens as described in the Declaration, she subjected supernatants from 19 selected hybridomas to a RET assay to identify monoclonal antibodies that <u>did not</u> inhibit fusion of HeLa-env_{LAI} with HeLa-CD4+ cells, using a selection criterion of less than 10% inhibition, but that <u>did</u> inhibit fusion of HeLa-env_{JR-FL} with PM1 cells, using a selection criteria of greater than 35% inhibition. As set forth in the attached Declaration, 8 of the 19 hybridomas tested, 4 of which are described in the subject application, produced monoclonal antibodies which met these selection criteria.

Similarly, in *In re Wands*, the monoclonal antibodies from 4 of 9 hybridomas tested fell within the claimed range (see pages 1405 and 1406, *In re Wands*), and the court concluded, based on this success rate, that <u>undue experimentation was not required</u> to practice the claimed invention. Applicants submit that their own success rate is comparable to the 44% success rate in *In re Wands*. For ease of

comparison, applicants provide the following table, which compares the pertinent facts in *In re Wands* with those applicable to the presently claimed invention:

	In re Wands	**Applicants**
Total no. of hybridomas produced	Not declared in case	2100
No. of hybridomas meeting first criterion*	143	200
No. of hybridomas selected for testing	9	19
No. of hybridomas meeting second criteria#	4	8
Percentage success	44%	42%

*First criterion: **In re Wands** - "high binders" - see p1405
Applicants - 33% or greater inhibition of fusion of Hela-Env_{JR-FL} with PM1

#Second criteria: **In re Wands** - (A) IgM and (B) binding affinity constant of at least 10^9M^{-1} - see p1405
Applicants - (A) inhibits the fusion of HeLa-Env_{JR-FL} and a CD4+ PM1 cell but (B) does not inhibit fusion of the HeLa-Env_{LAI} with a HeLa-CD4+ cell

In addition, in *In re Wands*, the CAFC found that "[t]here was a high level of skill in the art at the time when the [Wands] application was filed and all of the methods needed to practice the invention were well known." See *In re Wands* page 1406. Thus, the Court decided that even at the time of Wands' invention in 1980, undue experimentation would not have been required to practice the Wands' invention in the hybridoma/monoclonal antibody field. Applicants' earliest claimed effective date is June 7, 1995. Applicants contend that during the approximately 14½ years subsequent to the filing date in question in *In re Wands*, the hybridoma/monoclonal antibody field, became more predictable, not less predictable.

Accordingly, applicants maintain that, in light of the disclosure of the immunogen, the teachings and direction in the specification, the

working examples, the high level of skill in the art, the recited functional characteristics of the antibodies, the decision of *In re Wands*, and the established nature of the art at the time of filing the instant application, the subject matter of the pending claims is enabled. Accordingly, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Summary

Applicants respectfully request allowance of the claims as currently pending in the above-identified application.